REMARKS

Reopening of Prosecution After Appeal

The finality of the Office action mailed May 26, 2006 was withdrawn and the Examiner has reopened prosecution after appeal (see, Office Action mailed May 14, 2007, page 2, item 1). Applicants call the Examiner's attention to Section 1207.04 of the *Manual of Patent Examining Procedure* (*MPEP*) where it states that "[t]he examiner may, with approval from the supervisory patent examiner, reopen prosecution to enter a new ground of rejection after appellant's brief or reply brief has been filed." Such approval is evidenced by a statement that the Supervisory Patent Examiner approves of reopening prosecution and the Supervisory Patent Examiner's signature (see, *MPEP* § 1207.04).

Applicants note that the required statement and signature did not accompany the Office action mailed May 14, 2007. However, in an effort to advance prosecution, Applicants are proceeding with this reply based on the assumption that the Supervisory Patent Examiner did approve of reopening prosecution.

Status of the Claims

The Examiner lists claims 1-7, 13-19, 21-26, 30, 31, 38, 40, and 42 as pending (see, Office action, page 2, item 2). However, this is a list of the claims that were the subject of an Appeal Brief under 37 C.F.R. § 41.37, filed on November 15, 2006. Pursuant to 37 C.F.R. § 1.121(c), "[t]he claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application." Thus, Applicants submit that claims 1-7, 11-26, 28-31, and 38-43, as set forth in the Amendment After Final under 37 C.F.R. § 1.116, filed July 25, 2006, are in fact pending in the present application.

No new matter has been added by amendment. Reexamination and reconsideration of the claims are respectfully requested.

The Rejection of the Claims Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

Written Description

Claims 1-7, 13-19, 21-26, 30, 31, 38, 40, and 42 remain rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement of Section 112. The Examiner asserts that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. Specifically, the Examiner rejects those portions of the claims directed to isolated nucleotide sequences having at least 95% sequence identity to the coding sequence set forth in nucleotides 73-249 of SEQ ID NO:17 or nucleotides 64-240 of SEQ ID NO:14, where the nucleotide sequences encode polypeptides having pesticidal activity against insect pests of the Homopteran or Lepidopteran orders. This rejection is respectfully traversed.

As Applicants stated in their earlier-filed Amendment (filed July 25, 2006), in order to satisfy the written description requirement of 35 U.S.C. § 112, the application must reasonably convey to one skilled in the art that the applicant was in possession of the claimed subject matter at the time the application was filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Every species encompassed by the claimed invention, however, need not be disclosed in the specification to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. *Utter v. Hiraga*, 845 F.2d 993, 6 USPQ2d 1709 (Fed. Cir. 1988). The Federal Circuit has made it clear that sufficient written description requires simply the knowledge and level of skill in the art to permit one of skill to immediately envision the product claimed from the disclosure. *Purdue Pharm L.P. v. Faulding In.*, 230 F.3d 1320 1323, 596 USPQ2d 1481, 1483 (Fed. Cir. 2000) ("One skilled in the art must immediately discern the limitations at issue in the claims.").

Moreover, the "Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, ¶ 1, 'Written Description' Requirement" state that a genus may be described by "sufficient description of a representative number of species . . . or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties." 66 Fed. Reg. 1099, 1106 (2001). This is in accordance with the standard for written description set forth in *Regents*

of the University of California v. Eli Lilly & Co, 119 F.3d 1559 (Fed. Cir. 1997), where the court held that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, or chemical name' of the claimed subject matter sufficient to distinguish it from other materials." 119 F.3d at 1568, citing *Fiers v. Revel* 984 F.2d 1164 (Fed. Cir. 1993). In *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.2d 926 (Fed. Cir. 2002), the Federal Circuit adopted the PTO standard for written description, stating:

> [U]nder the Guidelines, the written description requirement would be met . . . if the functional characteristics of [a genus of polypeptides or nucleic acid molecules] were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed. We are persuaded by the Guidelines on this point and adopt the PTO's applicable standard for determining compliance with the written description requirement.

The claims of the present application meet the requirements for written description set forth by the Federal Circuit. All of the pending claims recite a functional limitation (*i.e.*, activity against insect pests of the Homopteran or Lepidopteran orders) and also require a predictable structure of a nucleotide sequence having at least 95% sequence identity to the coding sequence set forth in nucleotides 73-249 of SEQ ID NO:17 or nucleotides 64-240 of SEQ ID NO:14. Furthermore, the art and the specification provide standard assays that may be used to measure pesticidal activity (see, *e.g.*, Examples 5, 6 and 17). These requirements for function in combination with the recitation of a predictable structure should be sufficient to satisfy the written description requirement.

The Examiner asserts, however, that "[t]he pesticidal function is not specific" (Office action, page 3, lines 11-12). The terms "pesticidal activity" and "pesticidal polypeptides" are expressly defined in the specification at page 7, lines 12-19, where it states that the terms are used interchangeably and refer to "a property or activity of an organism or a substance, such as, for example, a polypeptide, that results in, but is not limited to, pest mortality, pest weight loss, pest attraction, pest repellency, and other behavioral and physical changes of a pest." Thus, contrary to the Examiner's assertion, the pesticidal function of the claimed polypeptides encoded by nucleotide variants having at least 95% sequence identity to the coding sequence of an *A.*

amoreuxi toxin are specific.

The Examiner further asserts that "[o]nly a portion of the structural features have been described - the percent identity to SEQ ID NO:14 or 17. But because this includes nucleic acids in which the protein sequence has a large number of amino acid substitutions, those amino acid substitutions that do not alter the function of the protein **must** be described" (Office action, page 5, lines 10-13; emphasis added). Applicants respectfully disagree with this assertion and submit that this is not the correct standard by which to judge compliance with written description requirements under 35 U.S.C. § 112, first paragraph. As the Board of Patent Appeals and Interferences has held, "[a]dequate description under the first paragraph of 35 U.S.C. 112 does not require *literal* support for the claimed invention .... Rather, it is sufficient if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an appellant had possession of the concept of what is claimed." *Ex parte Parks*, 30 USPQ2d 1234, 1236 (B.P.A.I. 1994) (citing *In re Anderson*, 471 F.2d 1237, 176 USPQ 331 (C.C.P.A. 1973)) (emphasis in original).

The claimed invention is directed to, *inter alia*, isolated pesticide-encoding nucleic acid molecules having at least 95% sequence identity to the coding sequence set forth in nucleotides 73-249 of SEQ ID NO:17 or nucleotides 64-240 of SEQ ID NO:14. The specification provides the nucleotide sequences (*i.e.*, the coding sequences of SEQ ID NOs:17 and 14) of a representative embodiment of the claimed sequences. Additionally, the sequences that fall within the scope of the claims (*i.e.*, at least 95% sequence identical to the coding sequence set forth in nucleotides 73-249 of SEQ ID NO:17 or nucleotides 64-240 of SEQ ID NO:14) can readily be identified by the methods set forth in the specification (*e.g.*, guidance for determining percent identity of sequences is provided in the specification on pages 23 through 28). Therefore, Applicants submit that the originally-filed disclosure conveys to one having ordinary skill in the art that Applicants had possession of the concept of what is claimed at the time of filing of the application, that is, isolated pesticide-encoding nucleic acid molecules having at least 95% sequence identity to the coding sequence set forth in nucleotides 73-249 of SEQ ID NO:17 or nucleotides 64-240 of SEQ ID NO:14.

In summary, adequate written description *does not* require literal support for the claimed

invention, rather, it is sufficient if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that Applicants had possession of the concept of what is claimed. Applicants submit that the relevant identifying physical and chemical properties of the disclosed genus would be clearly recognized by one of skill in the art and consequently, the Applicants were in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Accordingly, the rejection of claims 1-7, 13-19, 21-26, 30, 31, 38, 40, and 42 under 35 U.S.C. § 112, first paragraph, for lack of written description should be withdrawn.

Enablement

Claims 1-7, 13-19, 21-26, 30, 31, 38, 40, and 42 remain rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement of Section 112. Specifically, the Examiner asserts that the specification does not reasonably provide enablement for isolated nucleotide sequences having at least 95% sequence identity to the coding sequence set forth in nucleotides 73-249 of SEQ ID NO:17 or nucleotides 64-240 of SEQ ID NO:14, where the nucleotide sequences encode polypeptides having pesticidal activity against insect pests of the Homopteran or Lepidopteran orders. This rejection is respectfully traversed.

The Examiner is respectfully reminded that in order to satisfy the enablement requirement Applicants need not demonstrate that every pesticide-encoding nucleic acid molecule having at least 95% sequence identity to the coding sequence set forth in nucleotides 73-249 of SEQ ID NO:17 or nucleotides 64-240 of SEQ ID NO:14 encompassed by the claims could be used to successfully practice the invention, such that no experimentation would be required. According to the applicable case law, the test of enablement is not whether experimentation is necessary to make and use an invention, but rather if experimentation is necessary, whether it is undue. *In re Angstadt*, 198 USPQ 214, 219 (C.C.P.A. 1976). Furthermore, a considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The test of whether an invention requires undue experimentation is not based on a single

factor, but rather is a conclusion reached by weighing many factors. *Id.* at 1404. Factors to be considered in determining whether undue experimentation is required include the quantity of experimentation necessary, the amount of guidance provided in the specification, the presence of working examples of the invention in the application, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability in the art, and the breadth of the claimed invention. *Id.* Accordingly, the holding of *Wands* does not require that Applicants provide as working examples every pesticide-encoding sequence that could be used to practice the present invention. Rather, *Wands* sets out factors to be considered in determining whether undue experimentation is required to make and use the invention.

Applicants maintain that sufficient guidance for making and using the recited pesticide-encoding sequences is presented in the specification. The claims recite that the isolated nucleotide sequences have at least 95% sequence identity to the coding sequence set forth in nucleotides 73-249 of SEQ ID NO:17 or nucleotides 64-240 of SEQ ID NO:14. The claimed nucleotide sequences are further limited by the functional requirement that they encode polypeptides having pesticidal activity against insect pests of the Homopteran or Lepidopteran orders. The isolated nucleotide sequences recited in the present claims vary from a specific *A. amoreuxi* toxin sequence within structural parameters that are defined in the specification (*i.e.*, the nucleotide sequences share a specified percent identity with the coding sequence set forth in nucleotides 73-249 of SEQ ID NO:17 or nucleotides 64-240 of SEQ ID NO:14). Guidance for preparing variants of a nucleotide sequence encoding an *A. amoreuxi* toxin sequence, and for determining percent identity, are generally known in the art and are also provided in the specification. See, for example, page 16, line 21, continuing through page 18, line 5; page 18, line 6, continuing through page 19, line 28; and page 23, line 14, continuing through page 28, line 18. The necessary molecular biology and mutagenesis techniques for preparing the nucleotide variants of the invention are routine and described in the specification. Moreover, methods for assessing the pesticidal activity of a polypeptide are readily available in the art and provided in the specification. See, for example, Examples 5, 6 and 17. Although the Examiner has improperly discounted the guidance provided in the specification, the holding of *Wands* indicates that such factors are significant to and should be afforded considerable weight in any

enablement determination.

The Examiner has cited three additional references in support of the proposition that making amino acid substitutions in *A. amoreuxi* toxins (*e.g.*, SEQ ID NO:20) is unpredictable. First, the Examiner has cited Hammock *et al.* (WO 2003/028666) as disclosing four scorpion proteins from *P. transvaalicus* with 63-66% sequence identity to SEQ ID NO:20 and Herrmann *et al.* as disclosing four scorpion proteins from *B. judaicus* with 43-45% sequence identity to SEQ ID NO:20. It is unclear how these references support the Examiner's conclusion that making amino acid substitutions in *A. amoreuxi* toxins is unpredictable.

The Examiner has also cited Zeng *et al.* (*Peptides* 27:1745-54, 2006), asserting that this reference teaches that although a superfamily of scorpion toxins have similar primary structures, their biological activities are highly divergent (referring to page 1749, left-hand column). Applicants submit that the "highly divergent biological activities" referred to by Zeng *et al.* are not in fact "highly divergent." Rather, as Zeng *et al.* disclose, three of the referenced toxins are lethal to mice, two are potent but non-lethal to mice (one of which causes writhing), one is highly depressant, and one is devoid of toxicity when it is injected intracerebroventricularly (see, page 1749, left-hand column, lines 5-11). At best, the disclosure of Zeng *et al.* teaches that the route of administration of scorpion toxins to **mice** affects their activity in **mice**. As the pending claims are directed to *A. amoreuxi* toxins having pesticidal activity against insect pests of the Homopteran or Lepidopteran orders, it is unclear how this reference supports the Examiner's assertion that making amino acid substitutions in *A. amoreuxi* toxins is unpredictable.

The Examiner also asserts that the specification fails to provide guidance for which amino acids of SEQ ID NO:20 can be altered to maintain pesticidal but not mammalicidal activity, and which regions of the protein can tolerate modifications and still produce a functional protein (see, Office action, page 9, lines 3-7; page 10, lines 9-12; page 11, lines 7-11; and page 12, lines 3-6). In support of these assertions, the Examiner continues to cite Guo *et al.* (*Proc. Natl. Acad. Sci. USA* 101:9205-10, 2004) for the proposition that increasing the number of amino acid substitutions in a protein increases the probability that the protein will be functionally inactivated, and Lazar *et al.* (*Mol. Cell. Bio.* 8:1247-52, 1988) and Hill *et al.* (*Biochem. Biophys. Res. Comm.* 244:573-77, 1998) for the proposition that the art is generally unpredictable with

respect to modification of amino acid sequences.

Applicants submit that the Examiner's preoccupation with the potential mammalicidal activity of variants of SEQ ID NO:20 is misplaced, as the pending claims are directed to *A. amoreuxi* toxins and variants thereof having pesticidal activity against insect pests of the Homopteran or Lepidopteran orders. Furthermore, the Examiner has mischaracterized the Guo *et al.*, Lazar *et al.* and Hill *et al.* references. As Guo *et al.* make abundantly clear, their teachings are directed towards understanding the probability that a random amino acid replacement will lead to a protein's functional inactivation, in order to quantitate protein tolerance to random change (see, *e.g.*, the Abstract). Guo *et al.* term this probability the "x factor" and disclose a broadly applicable approach to calculate x factors. As detailed in the Amendment to the previous Office action (filed July 25, 2006), Lazar *et al.* and Hill *et al.* simply teach that alteration of **highly conserved** sequences will disrupt function. Neither the Guo *et al.* reference, the Lazar *et al.* reference nor the Hill *et al.* reference establishes that the experimentation needed to practice the claimed invention is undue. See, *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

In order to identify the pesticide-encoding sequences encompassed by the present claims, one of skill in the art would need only perform two steps. First, generate a nucleotide sequence having at least 95% sequence identity to the coding sequence set forth in nucleotides 73-249 of SEQ ID NO:17 or nucleotides 64-240 of SEQ ID NO:14. Second, assay the encoded polypeptide for functional activity. Such assays, while known in the art, have further been presented in the specification (see, *e.g.*, Examples 5, 6 and 17). Although some experimentation is required to practice the claimed invention, it is now customary in the art to generate a large number of sequences and to test them in large-scale assays for a desired function, and, therefore, such experimentation is not undue, particularly in view of the routine nature of the required methods. "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (C.C.P.A. 1971) (emphasis in original).

In light of the level of skill and knowledge in the art, the presence of working examples and the guidance provided in the specification, Applicants respectfully submit that the rejection of claims 1-7, 13-19, 21-26, 30, 31, 38, 40, and 42 under 35 U.S.C. § 112, first paragraph, for lack of enablement should be withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the rejections under 35 U.S.C. § 112, first paragraph have been overcome and the claims are in condition for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned attorney.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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